Amendments to the Specification:

Please replace the paragraph on page 1, beginning on line 6, with the following amended paragraph:

This application is a divisional of U.S. Application No. 09/451,489, filed November 30, 1999, which claims of the benefit of ~~derives priority from~~ U.S. Provisional Application No. 60/110,464, filed December 1, 1998. Commonly owned ~~copending USSN~~ U.S. Provisional Application No. 60/100,950 filed September 18, 1998, and ~~USSN~~ U.S. Application No. 60/075,783, filed February 22, 1998, ~~and WO 99/03852~~ are directed to related subject matter. Each of the above ~~application is~~ applications are incorporated by reference in its entirety for all purposes.

Please replace the paragraph beginning on page 4, line 27 with the following rewritten paragraph:

~~Fig. 7~~ Fig. 7 panels A-C depict BrdU and cK-18 Antibody Staining of HepG2 cells in xenograph embryos 48 hr after ~~transplantation~~ transplantation. ~~(A)~~ Fig. 7, panel A: Darkfield image showing the yolk and HepG2 cell mass location; ~~(B)~~ Fig. 7, panel B: Epifluorescence image of the same embryo using a rhodamine filter set indicates localization of CK18 to the cell mass. No CK18 staining was observed in the host tissue or in control embryos. ~~(C0~~ Fig. 7, panel C: Epifluorescence image of the same embryo using a fluorescein filter shows BrdU labelling in the HepG2 cell mass. Because the yolk is spherical most of the Brdu-labelled cells of the yolk syncytial layer are out of focus. The white arrow indicates host cells labelled with BrdU.

Please replace the paragraph beginning on page 5, line 3 with the following rewritten paragraph:

~~Fig. 8:~~ Fig. 8, panels A-C show that ~~Transplanted~~ transplanted HepG2 cells have tumor cell morphology. ~~(A)~~ Fig. 8, panel A: Brightfield image of a oblique sagittal section though a xenograft embryo. The notochord (NC) and anterior central nervous system (ANT.CNS) are labelled or orientation. ~~(B) and C)~~ Fig. 8, panels B and C: Higher magnification image of the cell mass and the anterior CAN. The nucleic of HepG2 cells are larger and lighter

in color than host nuclei. HepG2 cell masses comprise tightly packed cells that have little or no extracellular space.

Please replace the paragraph beginning on page 25, line 16 with the following rewritten paragraph:

All proliferating cells, including both the transplanted cells and the host cells, were labeled. Specifically to identify proliferating HepG2 cells, we performed a double labeling experiment using human specific anti-CK18 antibody. We detected BrdU and anti-CK18 using an FITC-conjugated secondary antibody and an RPE-conjugated secondary antibody, respectively. As described previously, transplantations were carried out using unlabeled HepG2 cells. 100 xenograft embryos in which HepG2 cell masses were visible were collected 24 hours after transplantation. A 3 μM solution of BrdU was then injected into the yolkball of 80 of the xenograft embryos. The embryos were then allowed to develop for an additional 24 hours before fixation and staining. Although the anti-BrdU antibody labeled both HepG2 cells and host cells, only HepG2 cells were labeled by both antibodies ~~(Fig. 7)~~ (Fig. 7, panels A-C). After BrdU injection, 72 of the 80 xenograft embryos contained cells labeled with both antibodies. In contrast, the control xenograft embryos, which were not injected with BrdU, contained only anti-CK-18 labeled cells. This experiment clearly shows that transplanted HepG2 cells proliferate in the zebrafish embryo. HepG2 cell masses in zebrafish embryo are histologically similar to xenograft HepG2 tumors in adult mice . To determine if the HepG2 cell masses were morphologically similar to tumors generated in the mouse models and their human counterparts, we performed a histologic examination of the xenograft embryos collected 24 and 48 hours post transplantation. Although the cell masses in the zebrafish embryo were smaller (100-300 μm in diameter) than tumors observed in mice (7-10 mm; Vucenik, et al., 1998), the general morphology of HepG2 cells in cell masses was similar (Klein, et al., 1989). Specifically, the HepG2 cells were round and had little cytoplasm ~~(Fig. 8)~~ (Fig. 8 panels A-C). The HepG2 cells were easily identifiable in tissue sections because the nuclei of the HepG2 cells were larger and more compact than the nuclei of zebrafish cells. In contrast to the host cells, the HepG2 cells were tightly packed with little or no extracellular space between cells. Cells with smaller nuclei,

presumed to be zebrafish cells, were also present in the HepG2 cell masses. There was no evidence of vacuolated space in any of the cell masses, which would suggest that the transplanted cells were dying.

Please replace the paragraph beginning at page 25, line 15 with the following rewritten paragraph:

To confirm that the transplanted HepG2 cells were viable, we examined xenograft embryos for the presence of human VEGF (hVEGF) and human AFP (hAFP), two proteins normally secreted by HepG2 cells in culture and to be present in the blood of patients diagnosed with hepatocellular carcinoma (Huber, 1985; Eraiser et al. 1998; Louha et al., 1997). High levels of hVEGF have also been correlated with adverse effects on heart development in zebrafish and other vertebrates (Drake, et al., 1995; Feucht, et al., 1997, Serbedzija, 1999). For these experiments, xenograft embryos were stained with human specific antibodies to either hVEGF or hAFP and these antibodies were detected using RPE labeled secondary antibodies. Because the fluorescence spectra of DiI and RPE are similar, transplantations were performed using unlabeled HepG2 cells. Embryos were collected 24 to 72 hours after transplantation. Transplanted cells exhibit appropriate cell characteristics including the production of proteins. 100% of the embryos stained for VEGF (100) contained labelled cells in cell masses. In addition, in 50% of hVEGF positive embryos, individual RPE-labeled cells were detected in close proximity to the cell mass. As was shown with hVEGF staining, 100% of the embryos stained for hAFP had labeled cells in the cell masses (Figure 5 ~~C and D~~). In contrast to hVEGF staining, in hAFP positive embryos, no cells were observed outside the cell mass, regardless of when the embryos were collected. For both hVEGF and hAFP antibodies, staining was restricted to HepG2 cells. Neither hVEGF nor hAFP label was observed in non-xenograft control embryos. Claim 61 was canceled.